Systematic review of randomised controlled trials of strategies to promote adherence to tuberculosis treatment

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Abstract

Objective: To determine the effectiveness of strategies to promote adherence to treatment for tuberculosis.
Identification: Searches in Medline (1966 to August 1996), the Cochrane trials register (up to October 1996), and LILACS (Literatura Latinoamericana y del Caribe en Ciencias de la Salud) (1982 to September 1996); screening of references in articles on compliance and adherence; contact with experts in research on tuberculosis and adherence.
Inclusion criteria: Randomised or pseudorandomised controlled trials of interventions to promote adherence with curative or preventive treatment for tuberculosis, with at least one measure of adherence.
Main outcome measure: Relative risks and 95% confidence intervals for estimates of effect for categorical outcomes.
Results: Five trials met the inclusion criteria. The relative risk for tested reminder cards sent to patients who defaulted on treatment was 1.2 (95% confidence interval 1.1 to 1.4), for help given to patients by lay health workers 1.4 (1.1 to 1.8), for monetary incentives offered to patients 1.6 (1.3 to 2.0), for health education 1.2 (1.1 to 1.4), for a combination of a patient incentive and health education 2.4 (1.5 to 3.7) or 1.1 (1.0 to 1.2), and for intensive supervision of staff in tuberculosis clinics 1.2 (1.1 to 1.3). There were no completed trials of directly observed treatment. All of the interventions tested improved adherence. On current evidence it is unclear whether health education by itself leads to better adherence to treatment.
Conclusions: Reliable evidence is available to show some specific strategies improve adherence to tuberculosis treatment, and these should be adopted in health systems, depending on their appropriateness to practice circumstances. Further innovations require testing to help find specific approaches that will be useful in low income countries. Randomised controlled trials evaluating the independent effects of directly observed treatment are awaited.

Introduction

From a fifth to a half of all patients with tuberculosis do not complete treatments lasting 24 months.[1] This failure risks prolonged infectiousness, relapse, drug resistance, and avoidable death. This is serious for both the patient and the community and is hindering attempts at global eradication.[1–3]

In recent years, experts have discouraged use of the term compliance with treatment as it has the "unfortunate connotation that the patient is docile and subservient to the provider."[4] To complete treatment is usually an independent choice of patients and best described as adherence. Recently, practitioners have recommended the term concordance to reflect "the active exchange of information, negotiation, and spirit of cooperation."[5]

Adherence requires accessible and appropriate health care, but even with such systems patients still do not always complete treatment. In the light of this, several specific strategies have been used.[1 6 7] Some aim to change the behaviour of health staff (training, motivation, and supervision). Others are directed at patients and include education, reminders and prompts to reattend, financial incentives to return, contracts between patient and provider, supervision of tablet taking, and tracing of patients who default. The purpose of this review is to examine the evidence from randomised controlled trials of the effectiveness of the various strategies to promote adherence.

Patients and methods

Criteria for selecting studies for the review

We included only randomised controlled trials or pseudorandomised trials (such as those using alternate allocation) that tested interventions aimed at promoting patient adherence to antituberculous treatment. Interventions were considered regardless of the intended target group or the setting. Studies of alternative drug types, schedules, doses, or routes of administration were excluded when the primary interest was to assess clinical effectiveness. At least one measure of adherence—for example, appointment keeping, drug collection, or drug taking—was required.

Search strategy

We searched the following electronic databases for relevant randomised controlled trials or previous reviews:

- Medline for 1966 up to August 1996. We used the search terms tuberculosis (in MeSH), patient-compliance (in MeSH), patient near compliance (in Ti or Ab), or adherence (in Ti or Ab), combined with the

See p 1407 and editorial by Squire and Wilkinson

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Medline search strategies for randomised controlled trials and reviews
- The database of abstracts of reviews of effectiveness and the Cochrane trials register[8]
- The Cochrane Collaboration's effective professional practice register of trials up to 14 October 1996
- The LILACS (Literatura Latinoamericana y del Caribe en Ciencias de la Salud) database for 1982 up to September 1996
- The specialist register of trials maintained by the Cochrane Infectious Diseases Group.

We scanned reference lists of all review articles and primary studies and contacted authors of included trials. We contacted experts in research on tuberculosis and adherence at the World Health Organisation, the International Union against Tuberculosis and Lung Diseases, and the United States Centers for Disease Control and Prevention.

Review procedures

We independently applied the inclusion criteria to all identified trials, resolving differences by discussion. We collected data on study methods, participants, interventions, and outcomes for each study. Quality of allocation concealment, allocation sequence generation, and follow up of subjects was assessed in each trial. The grading was a standard method of the Cochrane Infectious Diseases Group.[8] Analysis was through RevMan software,[9] and estimates of effect were summarised for categorical outcomes as relative risks with 95% confidence intervals.

Characteristics of included trials

Fourteen trials were identified, of which 5 met the inclusion criteria (see table). The number of participants in each trial ranged from 200 to 1300 patients, who had active tuberculosis,[10–12] were contacts of patients with tuberculosis and required prophylaxis,[11 13] or were contacts of patients with tuberculosis awaiting evaluation for active treatment or prophylaxis.[14]

Participants in three of the five studies were disadvantaged—namely, illiterate patients in Madras[10]; homeless people (mostly men) living in San Francisco, many of whom had a history of drug and alcohol misuse[14]; and patients with low income in Los Angeles, most of whom did not have English as their first language.[11] Interventions were not always directed at those who were receiving treatment. One study tested interventions on the mothers of children from state and private schools in Barcelona Province who had tested positive for tuberculin,[13] while another evaluated an intervention directed at the staff of tuberculosis clinics in Korea.[12]

Interventions examined were patient reminder cards,[10] patient education,[13] an incentive for patients,[14] help from peer group through community health workers,[14] a combination of patient education and incentive,[11] and intensive staff supervision.[12]

The commonest measure of adherence was completion of treatment (case holding). However, two trials assessed adherence to appointment keeping,[11 14] and two examined the use of drugs.[11 13] Only one study considered the outcome of treatment, and this was assessed as the rate of bacteriological conversion in those who initially had positive results on sputum microscopy or culture.[12]

In one trial, allocation was by case record number and was therefore not concealed.[11] For the remaining trials, adequacy of concealment could not be determined and information was also not available on the method used for generation of allocation sequence. With the exception of one study, in which 43 subjects (13.5%) could not be accounted for,[13] loss to follow up was not reported to have occurred. All the studies used an intention to treat analysis. None reported whether those assessing outcome were blinded to the intervention to which patients had been assigned.

Results

Six different strategies to promote adherence were tested in the trials included in this review (table). Up to two reminder letters sent to patients with tuberculosis soon after they had defaulted on clinic attendance produced good results. Of the 29 patients who defaulted in the intervention group, 17 (58.6%) returned, compared with 4 out of 31 (12.9%) in the control group. Even among illiterate patients rates of return were high.[10]

A monetary incentive ($5 (£3)) was highly effective in promoting adherence to an initial appointment for evaluation of tuberculosis among homeless people with positive results on tuberculin testing.[14] In the same study, recruits from the homeless community (so called peer health advisers) were paid to help patients keep their appointments, and this intervention was also effective compared with the control group. There was no statistical difference detected between the financial incentive and the peer adviser (table).

Health education given to mothers every three months improved compliance with chemoprophylaxis among children positive for tuberculin.[13] Each of three health education strategies was compared with no health education. Estimates of the effectiveness of the interventions in promoting attendance at the last clinic visit were better when the nurse visited or telephoned the patients at home than when health education was provide by a doctor at the clinic. The summary relative risk for the health education approaches compared with standard care (leaflet only) was 1.2 (95% confidence interval 1.1 to 1.4). Recent drug use assessed by the presence of a drug metabolite in a urine sample at the last clinic visit was significantly higher in each of the intervention groups compared with the controls.

One study compared a monetary incentive and health education with routine care.[11] The proportion completing treatment differed significantly between the intervention and control groups for patients receiving prophylaxis against tuberculosis but not for patients with clinical disease. As the confidence intervals overlapped substantially, however, no real difference may exist between the two odds ratios. Benefits were also found in terms of the average proportion of appointments kept and the mean proportion of drugs taken in this study.

Finally, an intervention directed at staff in tuberculosis clinics rather than patients was studied.[12] Patients with tuberculosis attending health centres with intense supervision of staff were more likely than those attending health centres with routine supervision of staff to complete treatment. The effect of the intervention on

Participants, design, interventions, and results of studies included in sytematic review of strategies to improve adherence to treatment for tuberculosis

Strategy	Study	Participants	Design	Interventions	Outcome: results	Relative risk (95% CI)
Reminder letters	Paramasivan et al 1993[10]	Patients with newly diagnosed tuberculosis in Madras; they were admitted for 1 month for education, motivation, and supervised treatment. After discharge treatment was self administered on an outpatient basis for 4 months	Random allocation without mention of concealment	(1) Reminder cards to patients who did not collect drugs (2) No follow up of patients who defaulted on collecting drugs	Completion of treatment: 88/100 (group 1), 73/100 (group 2)	1.2 (1.1 to 1.4)
Monetary incentive and peer advisers	Pilote et al 1996[14]	Homeless people, predominately men, in San Francisco, who were positive for tuberculin and being followed up. All received bus tokens	Random blocks of nine people; no mention of concealment	(1) Money ($5 (£3)) (2) Peer health adviser (3) Usual care	Attending first follow up appointment: 69/82 (group 1), 42/79 (group 3) 62/83 (group 2), 42/79 (group 3)	1.6 (1.3 to 2.0) 1.4 (1.1 to 1.8)
Health education	Sanmarti et al 1993[13]	Primary school children identified as positive for tuberculin on screening in Barcelona. Children with active tuberculosis were excluded	Random allocation of intervention; methods not stated	Education given: (1) During home visit from nurse (2) During telephone call by nurse (3) By doctor at clinic (4) In leaflet alone	Completing treatment: 75/79 (group 1), 55/77 (group 4) 75/80 (group 2), 55/77 (group 4) 64/82 (group 3), 55/77 (group 4)	1.3 (1.1 to 1.5) 1.3 (1.1 to 1.5) 1.1 (0.9 to 1.3)
Monetary incentive and health education	Morisky et al 1990[11]	Adults being treated for or receiving prophylaxis against tuberculosis in Los Angeles. Most were new immigrants to United States	Random allocation of intervention on basis of patients' record number	(1) Behavioural counselling in patient's language (10 minutes) plus money to complete treatment ($10 to cure tuberculosis, $5 for prophlaxis) (2) Usual care, with tracing of patients who defaulted	Completing preventive treatment: 37/58 (group 1), 16/59 (group 2) Completing treatment: 42/43 (group 1), 41/45 (group 2)	2.4 (1.5 to 3.7) 1.1 (1.0 to 1.2)
Intensive supervision of staff	Jin et al 1993[12]	Patients with newly diagnosed tuberculosis who were to be treated at primary healthcare facilities in Korea	Random allocation of 2 selected subcentres in each of the 7 health centres	(1) Intensive supervision and motivation of staff in tuberculosis clinics by senior doctors (2) Routine supervision of staff	Completing treatment: 513/651 (group 1), 423/649 (group 2)	1.2 (1.1 to 1.3)

bacteriological conversion (cure) rate was also favourable (relative risk 1.7 (1.4 to 1.9)).

Discussion

Systematic reviews of randomised trials of interventions to improve adherence to prescribed drug treatment[15] and compliance with appointment keeping[16] have recently been published. Our review differs from these in several ways.

Firstly, it concerns a single infectious disease and aims to find out which strategies are successful in promoting adherence to the comparatively long course of treatment required. Neither of the two recent reviews included studies of adherence to tuberculosis treatment as these failed to meet the selection criteria.

Secondly, adherence is defined broadly to cover all aspects of patient conformity to medical advice, including clinic attendance and taking drugs.

Thirdly, we included trials that measured adherence even when they did not measure the impact of the measure, such as on cure. Although in general Haynes et al are correct in stating that the ultimate purpose of improving adherence is to ensure clinical benefits,[15] in tuberculosis it seems reasonable to assume that patients who complete their treatment enjoy better health.

In general, the findings of the existing trials are encouraging as most strategies seemed to improve adherence. We could find no unpublished trials, and we cannot rule out the possibility of publication bias resulting in an overoptimistic view of the effects of the interventions.[17] Simple measures such as reminder letters sent to patients who defaulted were efficacious, even among illiterate patients.[10] A previous review also concluded that reminder letters are consistently useful in reducing broken appointments in several settings.[16]

Another strategy that holds promise is the use of peer help. The only trial that assessed the impact of lay health workers looked exclusively at adherence to a first appointment.[14] Further research is therefore needed to determine the full potential of this intervention. The use of money as an inducement to comply with medical advice might work in the short term but is problematic.[11 14] The global burden of tuberculosis is in poor countries where this strategy would be expensive and set precedents that could harm the work of health services in providing effective care for a range of conditions.

What the independent effect of health education is on adherence is difficult to determine from existing trials. In one study patients receiving health education were contacted or seen every 3 months while those in the control group were not.[13] The relative contributions of health education and increased attention are therefore hard to separate. Furthermore, in the study by Morisky et al health education was linked with a monetary incentive, so the independent roles of the interventions cannot be separated.[11] Lack of information in the study of intensive staff supervision[12] makes it difficult to determine the practicality of this strategy in other settings.

The measures of adherence to treatment used in most of the studies in this review were appointment keeping or completion of treatment (drug collections up to the end of the treatment course). The extent to which these intermediate outcomes correlate with actual drug taking is unknown. While two trials found good correspondence between clinic attendance and evidence of drug metabolites in the urine,[11 13] these measures are poor surrogates for regular drug taking.[18] The only study measuring treatment outcome did, however, show better clinic attendance and a higher cure rate in patients in the group in which staff were

intensely supervised compared with those in the control group.[12]

Directly observed treatment

One compliance enhancing strategy that is conspicuous by its absence among the trials we reviewed is directly observed treatment. In this scheme the patient takes the drugs in the presence of a healthcare provider or other designated person. We have recently become aware of two trials of this intervention. Self administered treatment with monthly follow up is currently being compared with treatment directly observed by a relative and by a peripheral worker in a study in Pakistan. In South Africa a trial has recently been completed comparing self administered treatment and treatment supervised in the community and at the specialist clinic. These and any other trials will be incorporated in subsequent editions of this review as they become available to us, provided that they meet the inclusion criteria.

Directly observed treatment has been successfully implemented in several settings and found to be associated with substantial improvements in rates of adherence and drug resistance.[6–23] However, it has usually been introduced as part of a comprehensive effort to improve tuberculosis services. The most common accompanying interventions are improved accessibility of services, increased availability of drugs, changes in drug regimens, patient incentives, tracing of patients who default, and outreach efforts.[24] Directly observed treatment may, therefore, simply be a marker for a more serious commitment to tuberculosis control. Carefully designed randomised trials evaluating the independent effects of directly observed treatment are awaited.

Implications for practice and research

We have found evidence for the effectiveness of several specific interventions to improve adherence to tuberculosis treatment. These should be implemented by health care providers when appropriate to local circumstances. Even simple interventions, such as reminder letters, are useful for helping to ensure that patients finish their treatment.

Many innovations for improving adherence to tuberculosis treatment exist, but only a few have been tested in randomised trials. To ensure relevance of interventions to settings in which most of the tuberculosis caseload occurs, studies in low income countries are a priority. Future research should measure adherence as well as clinical outcomes.

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Key messages

- Despite adequate delivery systems, some patients with tuberculosis do not complete treatment
- Six specific interventions have been tested in randomised trials to improve adherence, ranging from intensive staff supervision to monetary incentives for patients
- This systematic review of randomised trials found that all of the strategies tested seemed to improve adherence
- Independent effects of health education could not be assessed, and there are no trials yet available that test the effectiveness of directly observed treatment
- Health providers should draw on what is known to be effective when designing strategies appropriate to local needs and circumstances
- Further innovations, especially those that are feasible in developing countries, should be evaluated in randomised controlled trials before being introduced into routine practice.

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